Armed Forces College of Medicine

AFCM

Opioids – morphine 1

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INTENDED LEARNING OBJECTIVES (ILO)

By the end of this lecture the student will be able to:

1. Classify the types of opiate receptors
2. Explain mechanism of action of opiate receptors
3. Discuss the pharmacological actions of morphine
4. Interpret the therapeutic uses of MORPHINE
5. explain the adverse effects and contraindications of morphine
6. Identify the pharmacokinetics of morphine

Main Points

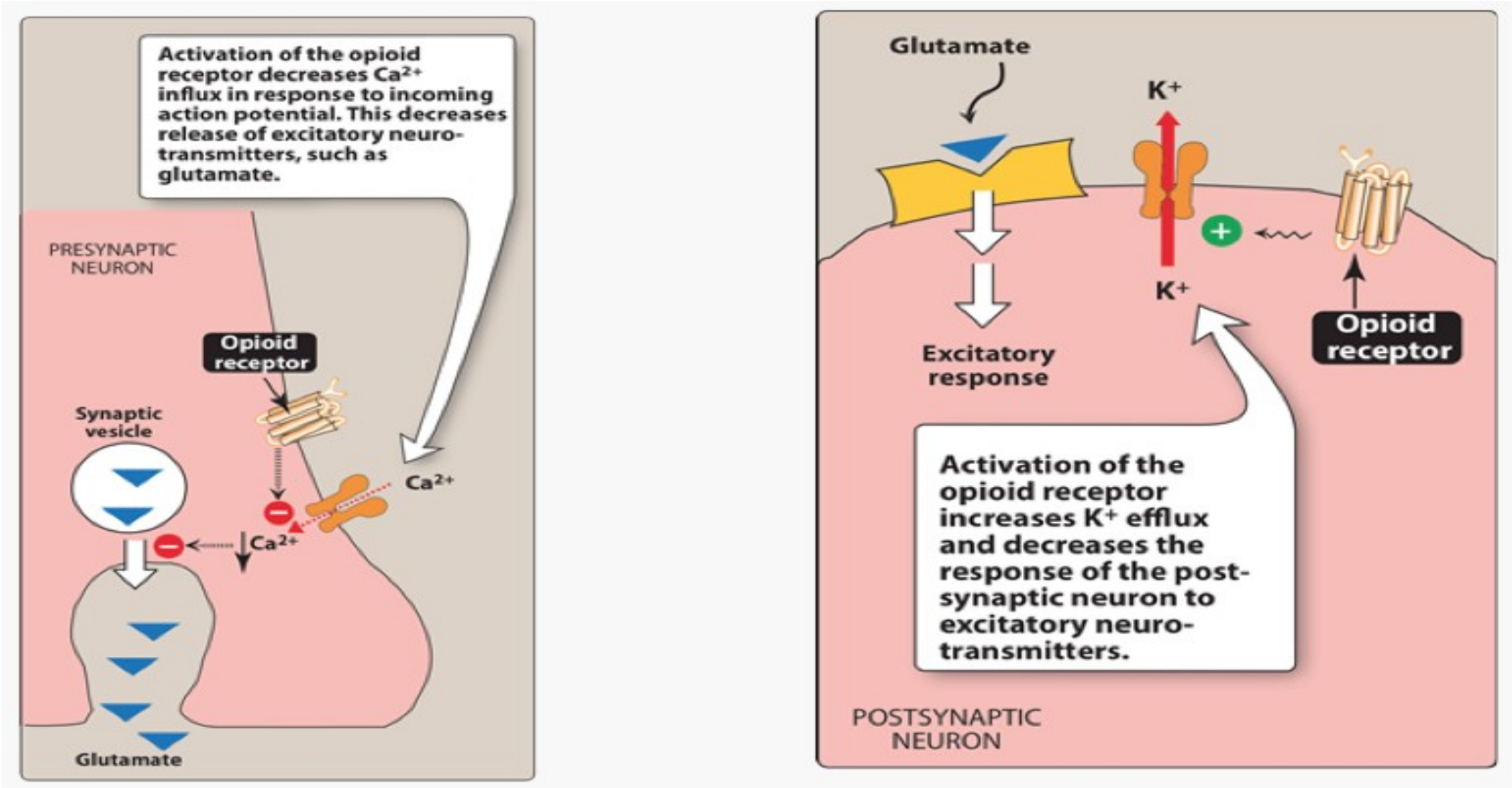
- Types of opiate receptors, and importance of mu and Kappa receptors
- Morphine has some stimulate actions, and some depressant actions on CNS
- Morphine causes miosis on the eye, and depression of respiratory center
- Contraindications and adverse effects of morphine are to be taken in consideration

Types of Opiate (Opioid) Receptors:

- **1- <u>Mu (μ_1 & μ_2)</u>:** Analgesia (Spinal & Supra-spinal), Euphoria, Sedation, Dependence, ↓ R.C., Miosis & Constipation.
- **2- <u>Kappa (κ_1, κ_2 & κ_3)</u>:** Analgesia (Spinal & Supra-spinal), Dysphoria, Psychotomimetic, Less ↓ R.C. & Less Miosis
- **3- <u>Delta (δ_1 & δ_2)</u>:** Analgesia (Spinal mainly) & Constipation.
- **4- <u>Sigma (σ)</u>:** Dysphoria & Hallucination.

Mechanism of Opiate (Opioid) Receptors:

- They are membrane receptors coupled to G-protein:
- 1- ⊖ Adenylate cyclase ⊖ ⊖ cAMP.
- 2- Open K^+-Channel ⊖ Hyperpolarization.
- 3- Block Ca^{2+}-Channel ⊖ ⊖ Release of transmitters & mediators.



Mechanism of action of μ-opioid receptor agonists in the spinal cord.

Endogenous Opio-peptides:

- 1- Endorphins (□-).
- 2- Enkephalins (Met- & Leu-)
- 3- Dynorphins (A- & B-).
- 4- Endomorphins

Actions Of Morphine:

- All actions of morphine are mediated via stimulation of Opiate receptors in C.N.S. & periphery.
- **C. N. S.:** Mixed Stimulation & Depression of certain parts of C.N.S.

Depressant Actions	Stimulant Actions
1-Analgesia all types of pain except itching 2-Narcosis 3- ⇩ R.C. → Hypoventilation & Hypoxia 4- ⇩ Cough center → Antitussive 5- ⇩ V.M.C. → Hypotension 6- ⇩ H.R.C. → Hypothermia 7- ⇩ Hormones: ACTH, FSH & LH.	1-Euphoria 2-Excitation in some females & Animals 3- ⇧ 3rd Cranial nerve → Miosis (PPP) 4- ⇧ Vagal center (CIC) → Bradycardia 5- ⇧ C.T.Z. (Small dose)→ Nausea & vomiting 6- ⇧ A.D.H. 7- ⇧ Monosynaptic spinal reflexes e.g. Stretch reflex

- **Analgesic effect of Morphine:**
- a- Effective in *All* types of pain *especially* Deep visceral pain.
- b- Not effective in itching. Morphine is a Histamine-releaser.

- **Eye** Miosis Pin Point Pupil (PPP)
- **V. S.** **Bradycardia & Hypotension**
  - Small therapeutic dose → No effect.
  - Large dose especially I.V. → Hypotension:
    - a- VMC & Vagal center (CIC)
    - b- Direct Venodilator effect.
    - c- Release of *Histamine* → V.D.
- **Respiratory System:**
  - R.C.
  - Cough center →Central Antitussive.
  - Histamine release →Bronchospasm especially in susceptible asthmatic patients.

- **<u>Smooth muscle</u>** **Spasmogenic** effect.
- **<u>G. I. T.</u>**
  - a- **Spasmogenic → Constipation**
  - b- All secretions (except salivary).
  - c- **<u>Loperamide & Diphenoxylate</u>** → Morphine-like on GIT → Constipation → Treat diarrhea with minimal or No CNS actions.

- **Skin:** Histamine release → Itching & Triple response.
- **Metabolism** → ⇩ B.M.R.
  - **NB) Tolerance to Morphine:**
    - 1- Occurs after continued use of Morphine for 10-14 days.
    - 2- Due to ⇩ Endogenous Endorphins & Enkephalins or ⇩ Adenylate cyclase expression.
    - 3- Affects *Mainly* Analgesia & ⇩ R.C. & *Not* PPP, constipation or excitation.
    - 4- Followed by dependence Both Psychic & Physical ⇨ Addiction.
    - 5- Cross Tolerance & Dependence between the Narcotic Analgesics.

- Which one of the following is an action of morphine?
  a. Stimulation of respiratory centre
  b. Spasmolytic effect on GIT
  c. Stimulation of vagal centre and bradycardia
  d. Depression of third cranial nerve
  e. Relief of itching pain

  The answer is C: Morhpine may cause bradycardia

Therapeutic Uses Of Morphine:

- **1- *P*ain:** Analgesic in *Severe Visceral Pain*
  - a- **C**ardiac pain e.g. Myocardial infarction
  - b- **C**ancer pain especially in terminal stages
  - c- **C**olic: Add Atropine in Biliary & Renal colic.
  - d- **B**one Fractures (Except Skull, Morphine is contraindicated in Head injury).
  - e- **P**ostoperative: Except Biliary & Eye operations.

- **2- *P*ulmonary Edema due to Acute Left Ventricular Failure:**
  - a- Venodilator → ↓ VR → ↓ E.D.V. → ↓ Preload & ↓ Pulmonary congestion.
  - b- Sedation → ↓ Sympathetic → Arterial V.D. → ↓ T.P.R. → ↓ After-load.
  - c- Slow respiration.
- **3- *P*rimary Neurogenic shock.**
- **4- *P*reanesthetic medication:** to provide analgesia, sedation & amnesia.

- One of the following is NOT an adverse effect of morphine:
  a. Physical and psychological dependence
  b. Constipation
  c. Respiratory depression
  d. Bronchoconstriction
  e. Hyperpyrexia
- **The Answer is E:** Morphine causes decreases in body temperature

Contraindications of Morphine:

- 1- Head injury:
  - a- Miosis → Interfere with proper diagnosis.
  - b- Morphine ⇩ R.C. → ⇧ CO_2 → Cerebral V.D. → ⇧ Synthesis of C.S.F. → ⇧ Intra-cranial tension → More ⇩ R.C.
- 2- ⇧ Intra-cranial tension.
- 3- Epilepsy.
- 4- Respiratory diseases e.g. Asthma & C.O.P.D.
- 5- Acute abdomen → Morphine → Analgesia → Interfere with proper diagnosis.
- 6- Pregnancy & Labor:
  - a- Pregnancy → Addict fetus → Withdrawal symptoms after labor.
  - b- Labor → Neonatal asphyxia.
- 7- Liver disease → Deficient metabolism.
- 8- Extremities of age → Deficient metabolism.

Adverse Effects of Morphine:

- 1- Interfere with proper diagnosis of Head injury & Acute abdomen.
- 2- ⇩ Respiration
- 3- PPP
- 4- Nausea & Vomiting
- 5- Bronchospasm
- 6- Constipation
- 7- Retention of urine
- 8- Neonatal asphyxia
- 9- Itching
- 10- Tolerance & cross-tolerance with other Opioids.

- *Morphine* causes enhanced parasympathetic stimulation to the eye, resulting in pinpoint pupils.

Kinetics of morphine

- **1- <u>Absorption</u>:**
  - a- Orally, *<u>But</u>* → Low (25 – 30 %) Oral Bioavailability.
  - b- Better absorbed after S.C. & I.M. injections.
  - c- In shock → Slow Diluted I.V. injection.
- **2- <u>Distribution</u>:** All over the body & passes BBB & Placental Barrier
  - a- During pregnancy → Addiction of Fetus.
  - b- During labor → Neonatal asphyxia → Treat by *<u>Naloxone</u>* (I.M. to mother before labor.

- **3- <u>Metabolism</u>:**
  - a- Extensive (70-75%) Hepatic First Pass Metabolism.
  - b- Conjugated with Glucuronic acid by Hepatic Microsomal Enzymes:

- **4- <u>Excretion</u>:**
  - Urine → *<u>Major</u>* route of excretion.

Lecture Quiz

Effects of morphine on CNS include all of the following <u>EXCEPT</u>:

Analgesia
Miosis
Respiratory depression
<u>Anticonvulsant effect</u>
Depression of cough reflex

Lecture Quiz

The use of morphine is contraindicated in all the following conditions EXCEPT:

Head injuries
Bronchial asthma
Acute left ventricular failure
Myxoedema
Biliary colic

To summarize:

- Type of opiate receptors
- Actions of morphine on CNS on the eye, on GIT and on the respiratory system.
- Contraindications and adverse effects of morphine

SUGGESTED TEXTBOOKS

1. Whalen, K., Finkel, R., & Panavelil, T. A. (2018) Lippincott's Illustrated Reviews: Pharmacology (7th edition.). Philadelphia: Wolters Kluwer

2. Katzung BG, Trevor AJ. (2018). Basic & Clinical Pharmacology (14th edition) New York: McGraw-Hill Medical.